Docket No.: PF-0049-2 DIV

Response Under 37 C.F.R. 1.116 - Expedited Procedure
Examining Group 1652

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By: _____ Printed: Lyza Finuliar

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Coleman et al.

Title:	A NOVEL HUMAN JAK2 KINASE		
Serial No.:	09/467,100	Filing Date:	December 10, 1999
Examiner:	Hutson, R.	Group Art Unit:	1652

Box AF
Commissioner for Patents
Washington, D.C. 20231

DECLARATION OF DR. TOD BEDILION
UNDER 37 C.F.R. § 1.132

I, TOD BEDILION, a citizen of the United States, residing at 132 Winding Way, San Carlos, California, declare that:

1. I was employed by Incyte Genomics, Inc. (hereinafter "Incyte") as a Director of Corporate Development until May 11, 2001. I am currently under contract to be a Consultant to Incyte Genomics, Inc.

2. In 1996, I received a Ph.D. degree in Cell, Molecular and Development Biology from UCLA. I had previously received, in 1988, a B.S. degree in biology from UCLA.

Upon my graduation from UCLA, I became, in April 1996, the first employee of Synteni, Inc. (hereinafter "Synteni"). I was a Research Director at Synteni from April 1996 until Synteni was acquired by Incyte in early 1998.

I understand that Synteni was founded in 1994 by T. Dari Shalon while he was a graduate student at Stanford University. I further understand that Synteni was founded for the purpose

of commercially exploiting certain "cDNA microarray" technology that was being worked on at Stanford in the early to mid-1990s. That technology, which I will sometimes refer to herein as the "Stanford-developed cDNA microarray technology", was the subject of Dr. Shalon's doctoral thesis at Stanford. I understand and believe that Dr. P.O. Brown was Dr. Shalon's thesis advisor at Stanford.

During the period beginning before I was employed by Synteni and ending upon its acquisition by Incyte in early 1998, I understand Synteni was the exclusive licensee of the Stanford-developed cDNA microarray technology, subject to any right that the United States government may have with respect to that technology. In early 1998, I understand Incyte acquired rights under the Stanford-developed cDNA microarray technology as part of its acquisition of Synteni.

I understand that at the time of the commencement of my employment at Synteni in April 1996, Synteni's rights with respect to the Stanford-developed cDNA technology included rights under a United States patent application that had been filed June 7, 1995 in the names of Drs. Brown and Shalon and that subsequently issued as United States Patent No. 5,807,522 (the Brown '522 patent). In December 1995, the subject matter of the Brown '522 patent was published based on a PCT patent application that had also been filed in June 1995. The Brown '522 patent (and its corresponding PCT application) describes the use of the Stanford-developed cDNA technology in a number of gene expression monitoring applications.

Upon Incyte's acquisition of Synteni, I became employed by Incyte. From early 1998 until late 1999, I was an Associate Research Director at Incyte. In late 1999, I was promoted to the position of Director, Corporate Development.

I have been aware of the Stanford-developed cDNA microarray technology since shortly before I commenced my employment at Synteni. While I was employed by Synteni, virtually all (if not all) of my work efforts (as well as the work efforts of others employed by Synteni) were directed to the further development and commercial exploitation of that cDNA microarray technology. By the end of 1997, those efforts had progressed to the point that I understand Incyte agreed to pay at least about $80 million to acquire Synteni. Since I have been employed by Incyte, I have continued to work on the further development and commercial exploitation of the cDNA microarray technology that was first developed at Stanford in the early to mid-1990s.

3. I have reviewed the specification of a United States patent application that I understand was filed on December 10, 1999 in the names of Roger Coleman et al. and was assigned Serial No. 09/467,100 (hereinafter "the Coleman '100 application"). Furthermore, I understand that this United States patent application was a divisional application of and claimed priority to United States patent application Serial No. 09/196,480 filed on November 19, 1998, which was itself a divisional application of and claimed priority to United States patent application Serial No. 08/567,508 filed on December 5, 1995 (hereinafter "the Coleman '508 application"), all having the identical specification. My remarks herein will therefore be directed to the Coleman '508 patent application, and December 5, 1995, as the relevant date of filing. In broad overview, the Coleman '508 specification pertains to certain nucleotide and amino acid sequences and their use in a number of applications, including gene expression monitoring applications that are useful in connection with (a) developing drugs (e.g., the diagnosis of inherited and acquired genetic disorders, expression profiling, toxicology testing, and drug development with respect to oncogenesis and cancer), and (b) monitoring the activity of drugs for purposes relating to evaluating their efficacy and toxicity.

4. I understand that (a) the Coleman '100 application contains claims that are directed to an isolated polynucleotide comprising a polynucleotide sequence selected from the group consisting of the polynucleotide sequence of SEQ ID NO:1 and a naturally occurring polynucleotide sequence having greater than 92% sequence identity to the polynucleotide sequence of SEQ ID NO:1, and (b) the Patent Examiner has rejected those claims on the grounds that the specification of the Coleman '100 application does not enable the use of the claimed naturally-occurring variants of the SEQ ID NO:1 polynucleotide. I further understand that whether or not a patent specification enables the use of its claimed subject matter is properly determined from the perspective of a person skilled in the art to which the specification pertains at the time of the patent application was filed. In addition, I understand that a substantial, specific and credible utility under the patent laws must be a "real-world" utility.

5. I have been asked (a) to consider with a view to reaching a conclusion (or conclusions) as to whether or not I agree with the Patent Examiner's position that the Coleman '100

application, and its grandparent the Coleman '508 application, do not provide an enabling disclosure for the use of the claimed naturally-occurring variants of the SEQ ID NO:1 polynucleotide, and (b) to state and explain the bases for any conclusions I reach. I have been informed that, in connection with my considerations, I should determine whether or not a person skilled in the art to which the Coleman '508 application pertains on December 5, 1995 would have concluded that the Coleman '508 application disclosed, for the benefit of the public, a specific beneficial use of the SEQ ID NO:1 polynucleotide and its naturally-occurring variants in their then available and disclosed form. I have also been informed that, with respect to the "real-world" utility requirement, the Patent and Trademark Office instructs its Patent Examiners in Section 2107.01 of the Manual of Patent Examining Procedure, 8th Edition, August 2001, under the heading I. Specific and Substantial Requirements, Research Tools:

> Many research tools such as gas chromatographs, screening assays, and nucleotide sequencing techniques have a clear, specific and unquestionable utility (e.g., they are useful in analyzing compounds). An assessment that focuses on whether an invention is useful only in a research setting thus does not address whether the specific invention is in fact "useful" in a patent sense. Instead, Office personnel must distinguish between inventions that have a specifically identified substantial utility and inventions whose asserted utility requires further research to identify or reasonably confirm.

6. I have considered the matters set forth in paragraph 5 of this Declaration and have concluded that, contrary to the position I understand the Patent Examiner has taken, the specification of the Coleman '508 patent application disclosed to a person skilled in the art at the time of its filing a number of uses for the claimed naturally-occurring variants of the SEQ ID NO:1 polynucleotide. More specifically, persons skilled in the art on December 5, 1995 would have understood the Coleman '508 application to disclose the use of the SEQ ID NO:1 polynucleotide and its naturally-occurring variants in a number of gene expression monitoring applications that were well-known at that time to be useful in connection with the development of drugs and the monitoring of the activity of such drugs. I explain the bases for reaching my conclusion in this regard in paragraphs 7-12 below.

7. In reaching the conclusion stated in paragraph 6 of this Declaration, I considered (a) the specification of the Coleman '508 application, and (b) a number of published articles

that evidence gene expression monitoring techniques that were well-known before the December 5, 1995 filing date of the Coleman '508 application. The published articles I considered are:

(a) Schena, M., Shalon, D., Davis, R.W., Brown, P.O., Quantitative Monitoring of Gene Expression Patterns with a Complementary DNA Microarray, Science, 270, 467-470 (October 20, 1995) (hereinafter "the Schena article") (copy annexed at Tab A);

(b) Sambrook, J., Fritsch, E.F., Maniatis, T., Molecular Cloning, A Laboratory Manual, pages 7.37 and 7.38, Cold Spring Harbor Press (1989) (hereinafter "the Sambrook Manual") (copy annexed at Tab B); and

(c) Xu, X., Kang, S.H., Heidenreich, O., Okerholm, M., O'Shea, J.J., Nerenberg, M.I., Constitutive activation of different Jak tyrosine kinases in human T cell leukemia virus type 1 (HTLV-1) tax protein or virus-transformed cells, Journal of Clinical Investigation, 96, 1548-55 (September 1995) (hereinafter "the Xu article") (copy annexed at Tab C).

8. The Schena article I considered (item (a) identified in paragraph 7) relates to work done at Stanford University in the early and mid-1990s with respect to the development of cDNA microarrays for use in gene expression monitoring applications under which Synteni became exclusively licensed. As I will discuss, a person skilled in the art who read the Coleman '508 application on December 5, 1995 would have understood that application to disclose the SEQ ID NO:1 polynucleotide and its naturally-occurring variants to be useful for a number of gene expression monitoring applications, e.g., as a probe for the expression of those specific polynucleotides in cDNA microarrays of the type first developed at Stanford.

9. Turning more specifically to the Coleman '508 specification, the SEQ ID NO:1 polynucleotide is shown at pages 35-39 as one of two sequences under the heading "Sequence Listing." The Coleman '508 specification specifically teaches that the "present invention relates to a novel human Jak2 kinase and to the use of the protein and its nucleic acid sequence in the study, diagnosis, prevention and treatment of diseases" and that the "assembled nucleotide sequence (SEQ ID NO: 1), hjak2, encodes the polypeptide (SEQ ID NO: 2), HJAK2." (Coleman '508 application at page 3). It further teaches that (a) the identity of the SEQ ID NO:1 polynucleotide was determined

from a placenta library (Coleman '508 application, page 3, line 27), and (b) the SEQ ID NO:1 polynucleotide encodes for the human Jak2 kinase (HJAK2) shown as SEQ ID NO:2 (Coleman '508 application at page 3, lines 29-31).

The Coleman '508 application discusses a number of uses of the SEQ ID NO:1 polynucleotide and its naturally-occurring variants in addition to their use in gene expression monitoring applications. I have not fully evaluated these additional uses in connection with the preparation of this Declaration and do not express any views in this Declaration regarding these additional uses. Consequently, my discussion in this Declaration concerning the Coleman '508 application focuses on the portions of the application that relate to the use of the SEQ ID NO:1 polynucleotide and its naturally-occurring variants in gene expression monitoring applications.

10. The Coleman '508 application discloses that the polynucleotide sequences disclosed therein, including the SEQ ID NO:1 polynucleotide, are useful as probes in chip (such as cDNA microarray) technologies. It further teaches that the chip technologies and the hjak2 nucleotide sequence:

> can be used in a diagnostic test or assay to detect disorder or disease processes associated with abnormal expression of hjak2. The nucleotide sequence is added to a sample (fluid, cell or tissue) from a patient under hybridizing conditions. After an incubation period, the sample is washed with a compatible fluid which optionally contains a reporter molecule which will bind the specific nucleotide. After the compatible fluid is rinsed off, the reporter molecule is quantitated and compared with a standard for that fluid, cell or tissue. If hjak2 expression is significantly different from the standard, the assay indicates the presence of disorder or disease. The form of such qualitative or quantitative methods may include northern analysis, dot blot or other membrane-based technologies, dip stick, pin or chip technologies, PCR, ELISAs or other multiple sample format technologies. (Coleman '508 application at page 14, lines 24-36).

The Schena article ("Quantitative Monitoring of Gene Expression Patterns with a Complementary DNA Microarray"; Tab A) was published prior to the December 5, 1995 filing date of the Coleman '508 application and describes the use of the Stanford-developed cDNA technology in a wide range of gene expression monitoring applications, including monitoring and analyzing gene expression patterns in tissues obtained from patients with "[a] wide variety of acute and chronic

physiological and pathological conditions" (Tab A, page 469). In view of the Coleman '508 application and the Schena article, persons skilled in the art on December 5, 1995 clearly would have understood the Coleman '508 application to disclose the SEQ ID NO:1 polynucleotide and its naturally-occurring variants to be useful in cDNA microarrays for the development of new drugs and monitoring the activities of drugs for such purposes as evaluating their efficacy and toxicity, as explained more fully in paragraph 11 below.

With specific reference to toxicity evaluations, those of skill in the art who were working on drug development on December 5, 1995 (and for many years prior to December 5, 1995) without any doubt appreciated that the toxicity (or lack of toxicity) of any proposed drug they were working on was one of the most important criteria to be considered and evaluated in connection with the development of the drug. They would have understood at that time that good drugs are not only potent, they are specific. This means that they have strong effects on a specific biological target and minimal effects on all other biological targets. Ascertaining that a candidate drug affects its intended target, and identification of undesirable secondary effects (i.e., toxic side effects), had been for many years among the main challenges in developing new drugs. The ability to determine which genes are positively affected by a given drug, coupled with the ability to quickly and at the earliest time possible in the drug development process identify drugs that are likely to be toxic because of their undesirable secondary effects, have enormous value in improving the efficiency of the drug discovery process, and are an important and essential part of the development of any new drug. Accordingly, the teachings in the Coleman '508 application, in particular regarding use of the SEQ ID NO:1 polynucleotide and its naturally occurring variants in differential gene expression analysis and in the development and the monitoring of the activities of drugs, clearly includes toxicity studies and persons skilled in the art who read the Coleman '508 application on December 5, 1995 would have understood that to be so.

11. A person skilled in the art on December 5, 1995, who read the Coleman '508 application, would understand that application to disclose the SEQ ID NO:1 polynucleotide and its naturally-occurring variants, to be highly useful as probes for the expression of those specific polynucleotides in cDNA microarrays of the type first developed at Stanford. For example, the specification of the Coleman '508 application would have led a person skilled in the art on December

5, 1995 who was using gene expression monitoring in connection with working on developing new drugs for the treatment of oncogenesis and cancer to conclude that a cDNA microarray that contained the SEQ ID NO:1 polynucleotide or its naturally-occurring variants would be a highly useful tool and to request specifically that any cDNA microarray that was being used for such purposes contain the SEQ ID NO:1 polynucleotide or its naturally-occurring variants. Persons skilled in the art would appreciate that cDNA microarrays that contained the SEQ ID NO:1 polynucleotide or its naturally-occurring variants would be a more useful tool than cDNA microarrays that did not contain the polynucleotides in connection with conducting gene expression monitoring studies on proposed (or actual) drugs for treating oncogenesis and cancer for such purposes as evaluating their efficacy and toxicity.

I discuss in more detail in items (a)-(f) below a number of reasons why a person skilled in the art, who read the Coleman '508 specification on December 5, 1995, would have concluded based on that specification and the state of the art at that time, that the SEQ ID NO:1 polynucleotide or its naturally-occurring variants would be a highly useful tool for inclusion in cDNA microarrays for evaluating the efficacy and toxicity of proposed drugs for treating oncogenesis and cancer, as well as for other evaluations:

(a) The Coleman '508 application teaches the SEQ ID NO:1 polynucleotide or its naturally-occurring variants to be useful as probes in cDNA microarrays of the type first developed at Stanford. It also teaches that such cDNA microarrays are useful in a number of gene expression monitoring applications, including "in a diagnostic test or assay to detect disorder or disease processes associated with abnormal expression of hjak2." (Coleman '508 application, page 14, lines 24-26; see paragraph 10, *supra*).

(b) By December 5, 1995, the Stanford-developed cDNA microarray technology was a well known and widely accepted tool for use in a wide range of gene expression monitoring applications. This is evidenced, for example, by the fact that, for over a year, the technology had provided the basis for the operations of an up-and-running company (Synteni), with employees, that was created for the purpose of developing and commercially exploiting that technology (see paragraphs 2, 8 and 10, *supra*).

(c) Based on the state of the art as of December 5, 1995, persons skilled in the art as of that date would have (a) concluded that the Coleman '508 application disclosed cDNA

microarrays containing the SEQ ID NO:1 polynucleotide or its naturally-occurring variants to be useful, and (b) readily been able to make and use such microarrays with useful results.

(d) The Coleman '508 specification contains a number of teachings that would lead persons skilled in the art on December 5, 1995 to conclude that a cDNA microarray that contained the SEQ ID NO:1 polynucleotide or its naturally-occurring variants would be a more useful tool for gene expression monitoring applications relating to drugs for treating oncogenesis and cancer than a cDNA microarray that did not contain the SEQ ID NO:1 polynucleotide or its naturally-occurring variants. Among other things, the Coleman '508 specification teaches that the identity of the SEQ ID NO:1 polynucleotide was determined from a placenta library. (Coleman '508 application, page 3, lines 24-27.) (See paragraph 9, *supra*).

Moreover, the Coleman '508 specification teaches that the HJAK2 protein having the amino acid sequence of SEQ ID NO:2 shares homology with known functional proteins. "HJAK2 has 92% similarity to murine Jak2 kinase (MUSPTK1; GenBank GI 409584; Wilks AF (1989) Proc Nat Acad Sci 86:1603-7) which in turn has 96% sequence similarity with human Jak1 kinase. These homologies and the conserved residues, G_{48}, K_{73}, E_{192}, and D_{220} which all lie within the catalytic domain contributed to the naming and uses of hjak2." (Coleman '508 application, page 3, lines 31-36.)

(e) Also pertinent is that a pre-December 5, 1995 article points to the role of Jak2 kinases, such as HJAK2, in oncogenesis and cancer. Xu et al. (Tab C) describe how "HTLV-1 infection causes an adult T cell leukemia in humans. The viral encoded protein tax, is thought to play an important role in oncogenesis." Xu et al. "show that a 130-kD cellular protein is constitutively phosphorylated in both Tax transformed mouse fibroblasts and HTLV-1 transformed human T cells" and identify the 130-kD protein "as Jak2 in tax transformed fibroblasts and Jak3 in HTLV-1 transformed human T cells." They conclude that "[p]hosphorylation of Jak2 in tax transformed cells resulted from high expression of IL-6" and that "**[c]onstitutive phosphorylation of Jak kinases may facilitate tumor growth in both HTLV-1 infected human T cells and the transgenic mouse model.**" (Tab C, page 1548, emphasis added.) Because of the relationship between the HJAK2 protein of SEQ ID NO:2 and known functional proteins stated above, and because those known functional proteins are important in the types of regulatory mechanisms implicated in oncogenesis and cancer, persons skilled in the art on December 5, 1995 would have considered SEQ ID NO:1

polynucleotide and its naturally-occurring variants to be important and valuable additions to a cDNA microarray for use in research into oncogenesis and cancer.

(f) Persons skilled in the art on December 5, 1995 would have appreciated (i) that the gene expression monitoring results obtained using a cDNA microarray containing a probe to the SEQ ID NO:1 polynucleotide or its naturally-occurring variants would vary, depending on the particular drug being evaluated, and (ii) that such varying results would occur both with respect to the results obtained from the probe described in (i) and from the cDNA microarray as a whole (including all its other individual probes). These kinds of varying results, depending on the identity of the drug being tested, in no way detracts from my conclusion that persons skilled in the art on December 5, 1995, having read the Coleman '508 specification, would specifically request that any cDNA microarray that was being used for conducting gene expression monitoring studies on drugs for treating oncogenesis and cancer (*e.g.*, a toxicology study or any efficacy study of the type that typically takes place in connection with the development of a drug) contain the SEQ ID NO:1 polynucleotide or one of its naturally-occurring variants as a probe. Persons skilled in the art on December 5, 1995 would have wanted their cDNA microarray to have a probe as described in (i) because a microarray that contained such a probe (as compared to one that did not) would provide more useful results in the kind of gene expression monitoring studies using cDNA microarrays that persons skilled in the art have been doing since well prior to December 5, 1995.

The foregoing is not intended to be an all-inclusive explanation of all my reasons for reaching the conclusions stated in this paragraph 11, and in paragraph 6, *supra*. In my view, however, it provides more than sufficient reasons to justify my conclusions stated in paragraph 6 of this Declaration regarding the Coleman '508 application disclosing to persons skilled in the art at the time of its filing adequate uses for the SEQ ID NO:1 polynucleotide and its naturally-occurring variants.

12. Also pertinent to my considerations underlying this Declaration is the fact that the Coleman '508 disclosure regarding the uses of the SEQ ID NO:1 polynucleotide and its naturally-occurring variants for gene expression monitoring applications is <u>not</u> limited to the use of those polynucleotides as probes in microarrays. For one thing, the Coleman '508 disclosure regarding the hybridization technique used in gene expression monitoring applications is broad (Coleman '508 application at, e.g., page 14, lines 24-36).

In addition, the Coleman '508 specification repeatedly teaches that the polynucleotides described therein (including the polynucleotide of SEQ ID NO:1) may desirably be used as probes in any of a number of long established "standard" non-microarray techniques, such as northern analysis, for conducting gene expression monitoring studies. See, e.g.:

(a) Coleman '508 application at page 6, lines 8-11) ("nucleic acid probes may be used in Southern, northern or in situ hybridizations to determine whether DNA or RNA encoding the protein is present in a biological sample, cell type, tissue, organ or organism.");

(b) Coleman '508 application at page 14, line 24 through page 15, line 13):

> Hjak2 nucleotide sequence can be used in a diagnostic test or assay to detect disorder or disease processes associated with abnormal expression of hjak2. The nucleotide sequence is added to a sample (fluid, cell or tissue) from a patient under hybridizing conditions. After an incubation period, the sample is washed with a compatible fluid which optionally contains a reporter molecule which will bind the specific nucleotide. After the compatible fluid is rinsed off, the reporter molecule is quantitated and compared with a standard for that fluid, cell or tissue. If hjak2 expression is significantly different from the standard, the assay indicates the presence of disorder or disease. The form of such qualitative or quantitative methods may include northern analysis, dot blot or other membrane-based technologies, dip stick, pin or chip technologies, PCR, ELISAs or other multiple sample format technologies.
>
> This same assay, combining a sample with the nucleotide sequence, is applicable in evaluating the efficacy of a particular therapeutic treatment regime. It may be used in animal studies, in clinical trials, or in monitoring the treatment of an individual patient. First, standard expression must be established for use as a basis of comparison. Second, samples from the animals or patients affected by a disorder or disease are combined with the nucleotide sequence to evaluate the deviation from the standard or normal profile. Third, an entirely new or pre-existing therapeutic agent is administered, and a treatment profile is generated. This posat-treatment [*sic*: post-treatment] assay is evaluated to determine whether the patient profile progresses toward or returns to the standard pattern. Successive treatment profiles may be used to show the efficacy of treatment over a period of several days or several months.

(c) The "Sambrook et al." reference is a reference that was well known to persons skilled in the art on December 5, 1995. A copy of pages from that reference manual, which was published in 1989, is annexed to this Declaration at Tab B. The attached pages from the Sambrook manual provide an overview of northern analysis and other membrane-based technologies for conducting gene expression monitoring studies that were known and used by persons

skilled in the art for many years prior to the December 5, 1995 filing date of the Coleman '508 application.

A person skilled in the art on December 5, 1995, who read the Coleman '508 specification, would have routinely and readily appreciated that the SEQ ID NO:1 polynucleotide and naturally-occurring variants disclosed therein would be useful as a probe to conduct gene expression monitoring analyses using northern analysis or any of the other traditional membrane-based gene expression monitoring techniques that were known and in common use many years prior to the filing of the Coleman '508 application. For example, a person skilled in the art on December 5, 1995 would have routinely and readily appreciated that the SEQ ID NO:1 polynucleotide and its naturally-occurring variants would be a useful tool in conducting gene expression analyses, using the northern analysis technique, in furtherance of (a) the development of drugs for the treatment of oncogenesis and cancer, and (b) analyses of the efficacy and toxicity of such drugs.

13. I declare further that all statements made herein of my own knowledge are true and that all statements made herein on information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, and that willful false statements may jeopardize the validity of this application and any patent issuing thereon.

Tod Bedilion

Signed at Redwood City, CA
this 9th day of May, 2002